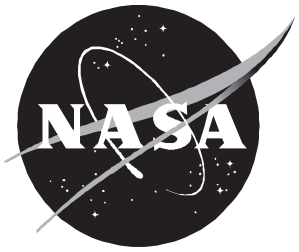
NASA Technical Paper 3453



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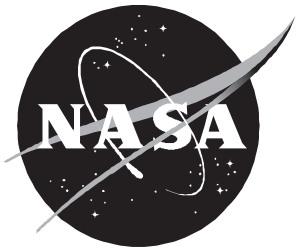

Estimates of Cellular Mutagenesis From Cosmic Rays

Francis A. Cucinotta and John W. Wilson
Langley Research Center • Hampton, Virginia

National Aeronautics and Space Administration
Langley Research Center • Hampton, Virginia 23681-0001

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Abstract

A parametric track structure model is used to estimate the cross section as a function of particle velocity and charge for mutations at the HGPRT locus in human fibroblast cell cultures. Experiments that report the fraction of mutations per surviving cell for human lung and skin fibroblast cells indicate small differences in the mutation cross section for these two cell lines when differences in inactivation rates between these cell lines are considered. Using models of cosmic ray transport, the mutation rate at the HGPRT locus is estimated for cell cultures in space flight and rates of about 2 to 10 $\times$ 10^{-6} per year are found for typical spacecraft shielding. A discussion of how model assumptions may alter the predictions is also presented.

Introduction

The level of biological injury to be expected from galactic cosmic rays (GCR) during prolonged manned spaceflight is difficult to estimate because of the lack of human data from exposures to high charge and energy (HZE) particles. Experimental studies for estimating the risk from long-term GCR exposures would include track segment irradiations with HZE particles in which animals or cell cultures are used. The most useful end points for such studies with animals are cancer induction and mortality. Cellular studies using cytoxicity as an end point are useful for providing estimates of the relative biological effectiveness (RBE), whereas the stochastic end points of mutagenesis or neoplastic transformation provide additional information on the late effects that may be useful in extrapolations of the level of risk for man and on the underlying mechanisms of damage from HZE particles.

Currently, experimental data are lacking on the understanding of stochastic effects from HZE exposures. Information is needed on protracted exposures typical of the GCR (from 15 to 20 cGy/yr), cellular and repair kinetics at low dose rates, and the change in damage induction over the broad range in charge and velocity that the GCR encompasses. Presently, no mechanistic models of radiation action capable of following the initial events for HZE exposures to the expression of stochastic effects in cells or animals are in existence. Because of the low dose rates that occur in space, single-particle effects from the highly ionizing component of the GCR are expected to dominate any deleterious effects. The action cross section, defined as the probability per unit fluence for the expression of the biological end point, is expected to be a useful approach for describing biological effects from the GCR; however, few theoretical models have been developed for predicting the action cross section at this time (ref. 1).

An experimental assay has been developed for studies of mutations at the hypoxanthine guanine phosphoribosyl transferase (HGPRT) locus in mammalian cell cultures. The HGPRT gene is located on the X chromosome, and the mutation of this gene is expected to be related to DNA (deoxyribonucleic acid) damage. However, the HGPRT mutant is noted to be more likely an expression of chromosome deletions or rearrangements rather than point mutations. (See ref. 2.) This assay system has been used by several groups (refs. 3–7) with a variety of exposure types in several cell lines. One of the shortcomings of this assay system is that the chromosome involved is necessary for cell replication, which results in the loss of potential mutants (ref. 8). Human-hamster hybrid systems are being used to obtain higher mutation rates in other studies (ref. 8). Also, measurements of Kronenberg and Little (ref. 5) of mutations to trifluorothymidine resistance locus indicate slow-growth mutants that are not typical of the HGPRT mutants, an indication that some variability exists in mutations at specific genetic loci in human cells.

The dynamic range of experimental data for HGPRT mutations suggests that the action cross section for this mutation can be estimated as a function of an ion charge and velocity. The parametric track structure model of Katz et al. (refs. 9–11) has been repeatedly successful in modeling the action cross section. The track structure model correlates the damage produced by gamma rays with ions through the radial distribution of dose from delta-ray production along the ions track. The action cross section parameterized from gamma-ray and track segment irradiations with several ion types has been shown to reproduce (in an unmodified form) experiments with other exposure types and dose ranges for specific end points (refs. 9–11).

In this report we examine whether a unique cross section can be extracted for HZE particles

by using reported experimental measurements for human cells. The modifying factors from experimental protocol for sparsely ionizing ions and the influence of cell survivability on measurements are important factors in the parametric modeling of the action cross section for HGPRT mutations. A linear kinetics model that contains a description of track structure effects has been developed (refs. 12 and 13) that considers the effects of multiple lesions or competing end points and utilizes the action cross section of Katz. The kinetics model of Wilson and Cucinotta (ref. 13) also includes repair/misrepair effects in a parametric formalism, and it is able to describe dose-rate effects. In the remainder of this report we consider the experimental data for human fibroblast cells (refs. 3, 6, and 7) in order to estimate the mutation cross section for the HGPRT gene. The cosmic ray transport code HZETRN (ref. 14) is then used to consider the expected mutation rates per year at solar minimum during space flight. The possible influences of repair processes on the mutation-rate estimates are then discussed in the context of this simple model. The calculations that we discuss for space flight are an attempt to quantify the expected damage rates from GCR for cell mutations when using existing models. Estimates for other stochastic end points will be discussed in future work.

Estimating the HGPRT Cross Section

The equations for cell survival in the Katz model or in the kinetics model have been discussed in the aforementioned references and will not be repeated here. Our only concern will be the linear components (initial slopes) of these models for parameterizing radiation action from the GCR. For cell mutation, the kinetics model is used because the effects of losses in the cell population are important at the high dose levels reported and therefore may affect estimates of initial slopes for mutation response. The action cross section in the track structure model is calculated as

$$\sigma = 2\pi \int_0^{T_{\max}} t\, dt\, P(t) \tag{1}$$

(ref. 9) where t is the radial distance along the ions track to a sensitive site of radius a_0, $T_{\max}$ is the maximum range of secondary electrons, and $P(t)$ is a probability function that is assumed to be of the multitarget or multihit form. For example, in the multitarget model the expression is

$$P(t) = \left(1 - e^{-\overline{D}(t)/D_0}\right)^m \tag{2}$$

where m is the target number and $\overline{D}$ is the average dose in the sensitive site assumed to be a short cylinder of radius a_0, which is evaluated using the radial-dose description described in reference 15. The cross section is observed to plateau at a value denoted by σ_0, which is indicative of an effective damage area inside the cell nucleus. In the track structure model, the fraction of an ions energy, $1 - (\sigma/\sigma_0)$, is assumed to be available to act through intertrack effects in a manner similar to gamma rays. At large velocities, σ is efficiently parameterized as

$$\sigma = \sigma_0\left[1 - \exp(Z^{*2}/\kappa\beta^2)\right]^m \tag{3}$$

where Z^* is the effective charge number of an ion, β is the velocity, and κ is a parameter related to a_0 and D_0. (See ref. 9.) We estimate the low-LET (linear energy transfer) or gamma-ray-like fraction for mutations from the GCR in our calculations below.

Experiments by Tsuboi et al. (refs. 6 and 7) using primary normal human skin fibroblasts were performed at the BEVALAC facility at the Lawrence Berkeley Laboratory for gamma rays and several relativistic ions with cytoxicity and mutations per surviving cell that were scored at several dose levels for each exposure type. In table 1 we list the beam energy and measured residual range from this

Table 1. Exposure of Skin Fibroblast Cells

Beam	Beam energy, MeV/amu	Measured residual range, cm	LET, keV/μm	Energy at irradiation, MeV/amu
^{20}Ne	670	30.7	25	600
^{40}Ar	570	13.4	95	480
^{40}Ar	330	3.4	150	207
^{56}Fe	600	7.4	200	425
^{56}Fe	400	2.2	300	210
^{56}Fe	300	.6	500	96
^{139}La	600	2.3	920 ([a]1136)	305

[a]LET differed more than 10 percent from values in references6 and 7.

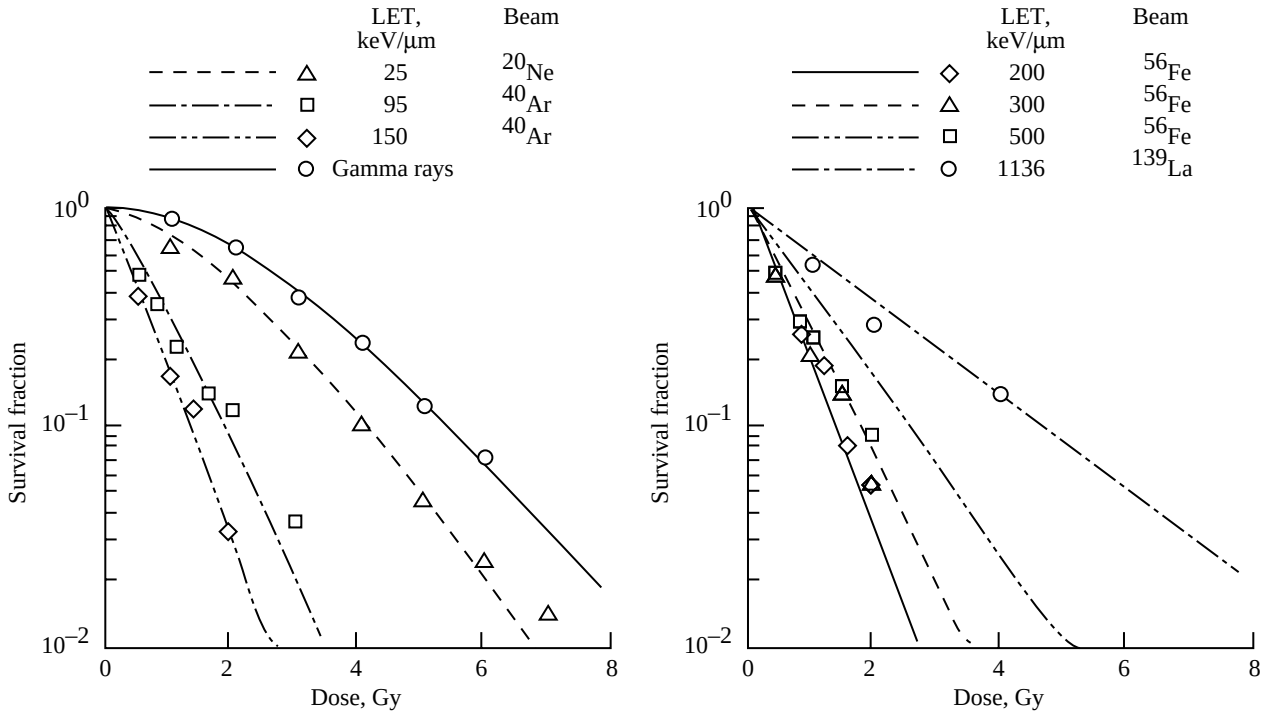


Figure 1. Comparison of model fits to experiment (refs. 6 and 7) for cell survival versus absorbed dose from gamma-ray and heavy ion exposure in human skin fibroblast cells.

experiment along with the LET reported and the energy at the cell cultures using the range-stopping power relations described by Wilson et al. (ref. 14). In the LET column of table 1, the LET estimated for the ^{139}La exposure is listed in parenthesis because it differed more than 10 percent from that reported by Tsuboi et al. in references 6 and 7. The ^{56}Fe exposure of 500 keV/μm is of note because the beam energy of 300 MeV/amu has been downgraded to 96 MeV/amu and the effects of nuclear fragmentation are expected to be substantial, i.e., the exposure is not of the track segment type.

In figure 1 the fit to the survival data from Tsuboi et al. (refs. 6 and 7) shows excellent agreement for all ions except the ^{56}Fe exposure at 500 keV/μm. The ^{139}La exposure is found to be less effective than all other ions on a per-dose level and to be nearly the same when treated on a per-fluence scale (refs. 6 and 7). Figure 2 compares the model fits with the experimental data, and good agreement is found for all ion types except for ^{56}Fe at 500 keV/μm and for ^{139}La at 1136 keV/μm. The calculations do find a reduced effectiveness for ^{139}La compared with the other ions studied, but not below the gamma-ray exposure found in the experiment. The importance of this discrepancy for cosmic ray exposures is expected to be small because ion fluences above a charge number (Z) greater than 28 are negligible in the GCR.

Table 2. Exposure of Lung Fibroblast Cells

Beam	LET, keV/μm	Energy at irradiation, MeV/amu
^{4}He	20	9.05
^{4}He	28	5.95
^{4}He	50	2.82
^{4}He	70	1.77
^{4}He	90	1.23
^{10}B	110	10.5
^{10}B	160	6.55
^{10}B	200	4.87
^{14}N	470	3.47

The experiment of Cox and Masson (ref. 3) for mutations in human lung diploid fibroblasts used low-energy ^{4}He, ^{10}B, and ^{14}N exposures. In table 2 we use the reported LET values for these ions to estimate their energies. The relatively small velocities of these ions indicates that they are in the track-width regime in which the cross section changes rapidly with the ion velocity. In figure 3 comparisons of survival level versus dose are given. The small or nonexistent shoulder for the low-LET ions can be

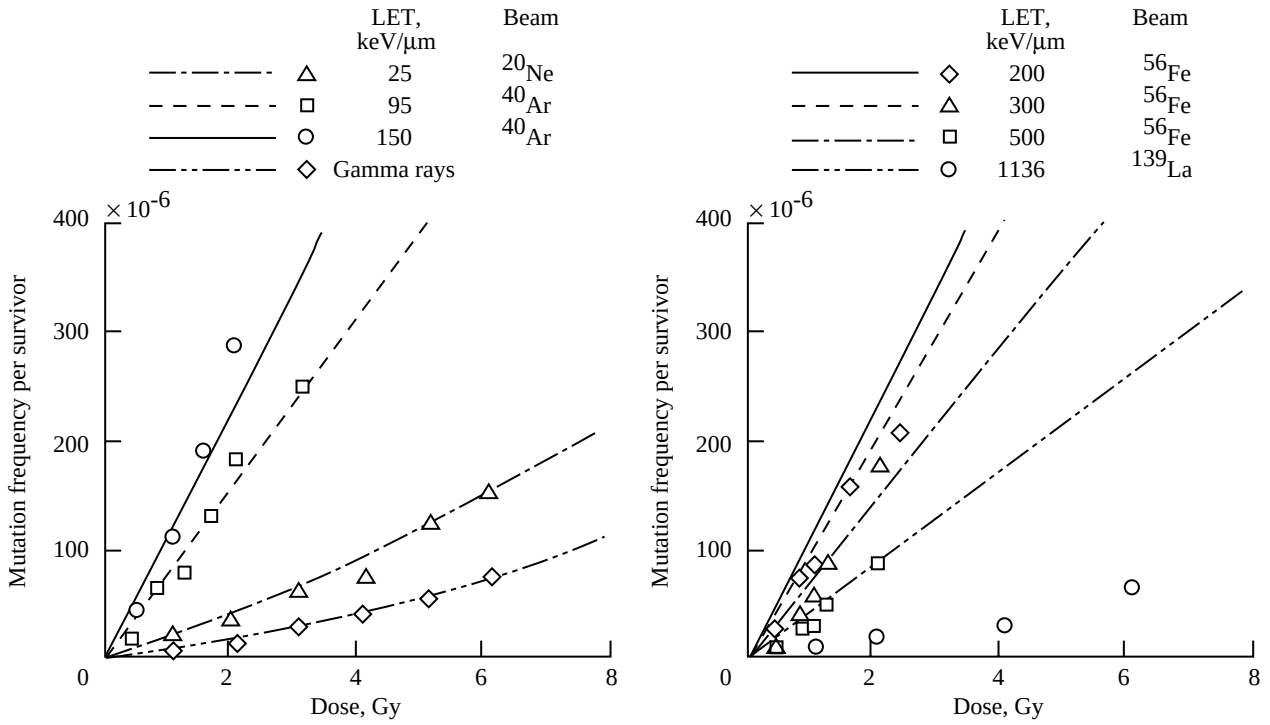


Figure 2. Comparison of model fits to experiment (refs. 6 and 7) for HGPRT mutations versus absorbed dose from gamma-ray and heavy ion exposure in human skin fibroblast cells.

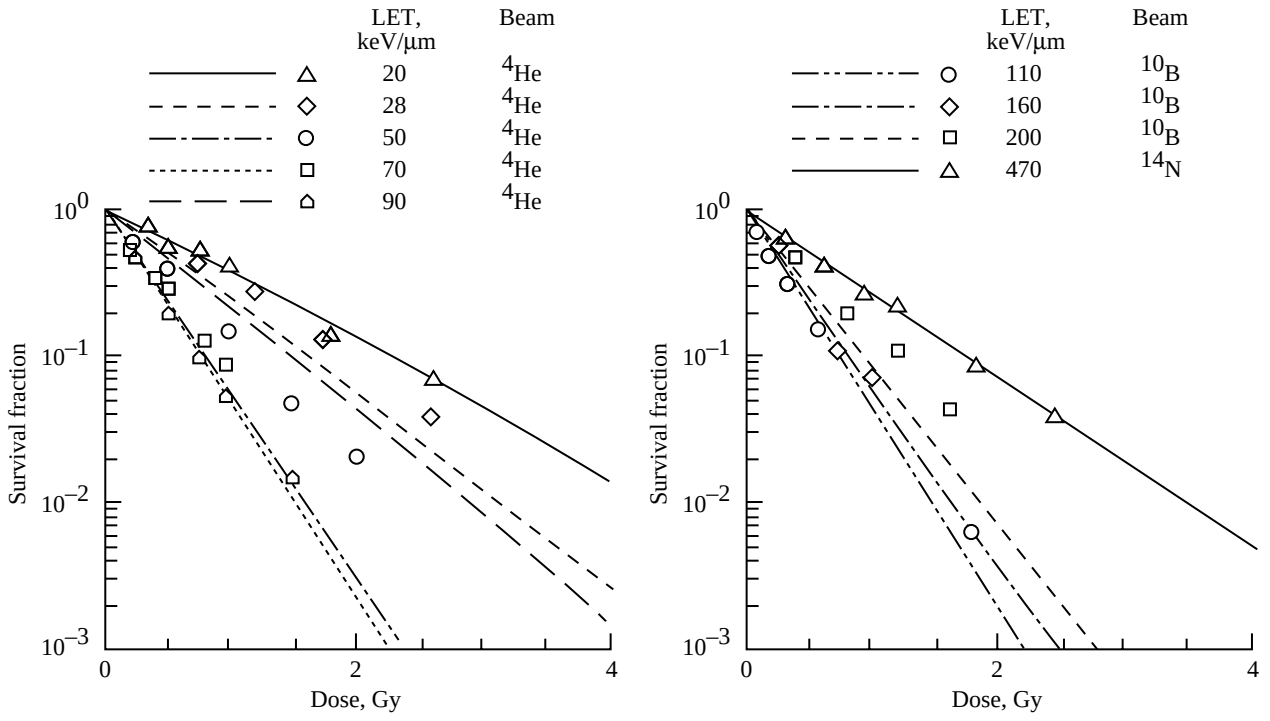


Figure 3. Comparison of model fits to experiment (ref. 3) for cell survival versus absorbed dose from heavy ion exposure in human lung fibroblast cells.

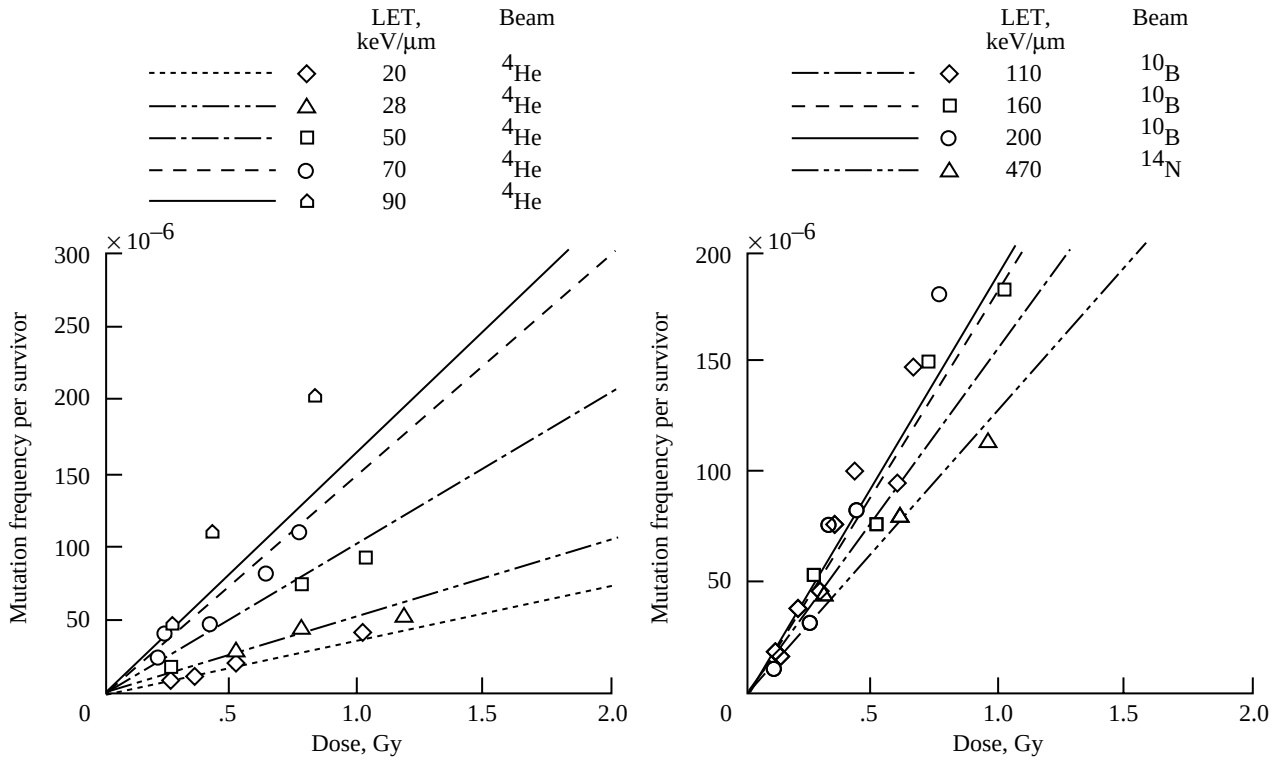


Figure 4. Comparison of model fits to experiment (ref. 3) for HGPRT mutations versus absorbed dose from heavy ion exposure in human lung fibroblast cells.

modeled by using a small value of D_0 for gamma rays in the Katz model or by assuming repair deficiency in the kinetics model. Agreement between calculations and experiment is good except for the data at 90 keV/μm in which the cross section has entered into the thin-down regime where the maximum delta-ray range is less than the value of a_0. In figure 4 the mutations per survival are shown in comparison with the experiment of Cox and Masson (ref. 3). In general, the agreement is good except for the ^{4}He data at 90 keV/μm in which, as mentioned above, the survival rate is underestimated.

Table 3 lists the cellular response parameters used to fit the above data sets. The inactivation parameters listed are similar to those found in other cell lines (ref. 9). We note that the parameters describing the action cross section for mutations in the skin and lung cells are nearly identical. Figure 5 compares the cross sections for mutations and inactivation for the skin fibroblasts for several ion types versus the energy of the ion. Note that the smaller site size for the mutations causes the thin-down regime to occur at smaller velocities than for the inactivation cross section, a result that may have important consequences for certain types of exposures such as the hydrogen recoils from neutrons. Figure 6 shows an effective

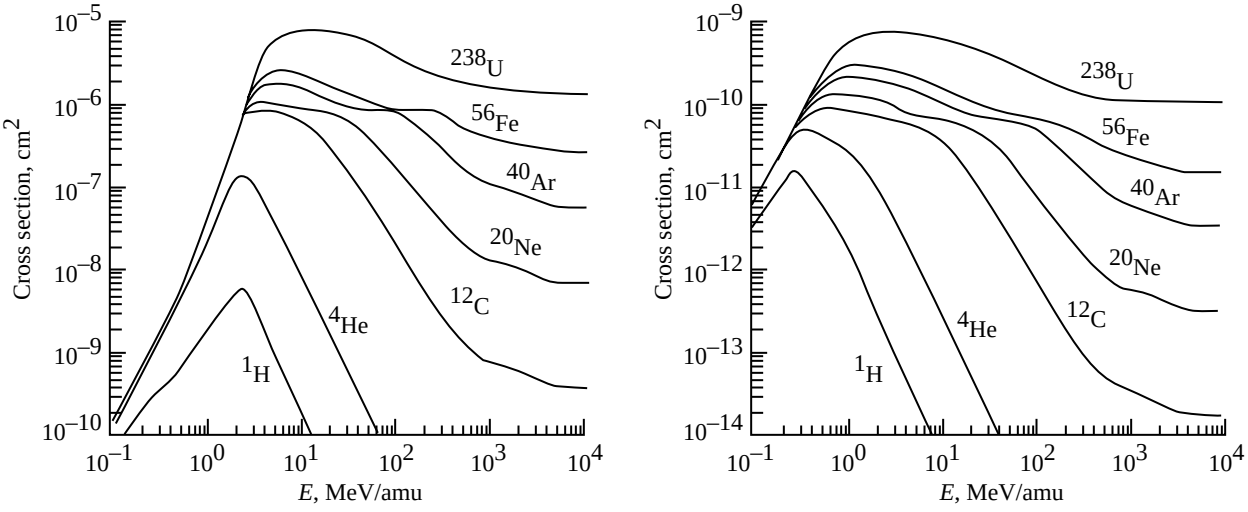
Table 3. Cellular Response Parameters

(a) Track structure parameters

End point	σ_0, cm^2	κ	a_0, nm	m	D_0, Gy
Human skin					
Inactivation . . .	8.9×10^{-7}	680	790	3	2.1
Mutation	6.2×10^{-11}	700	34	3	1250
Human lung					
Inactivation . . .	9.5×10^{-7}	500	620	3	2.4
Mutation	9.0×10^{-11}	750	40	3	950

(b) Repair efficiencies

End point	Repair efficiencies at values of i of—		
	1	2	$\geq m$
Human skin			
Inactivation	0.990	0.950	0
Mutation	0.995	0.990	0
Human lung			
Inactivation	0.7	0.25	0
Mutation	0.990	0.980	0



(a) Inactivation.

(b) HGPRT mutations.

Figure 5. Action cross sections plotted against ion energy of human skin fibroblast cells.

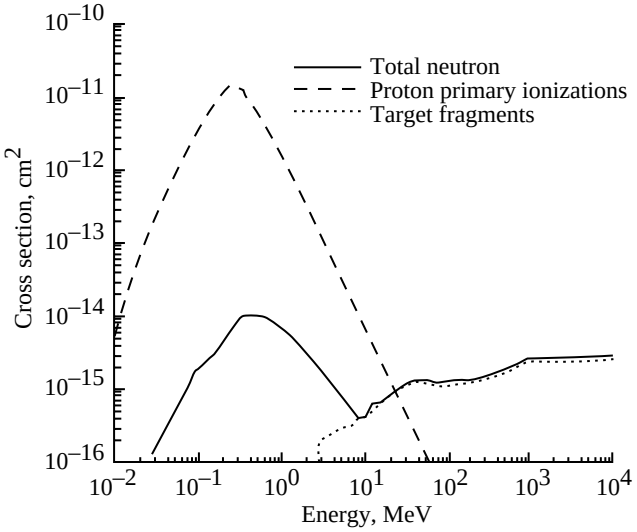


Figure 6. Action cross section versus energy for neutrons and protons for HGPRT mutations in human skin fibroblast cells. Dashed line denotes calculations for protons, dotted line denotes calculations for summed effects of target fragments produced in tissue-equivalent material, and solid line denotes effective neutron action cross section which includes elastic recoils and target fragments.

action cross section for neutrons in which the effects of secondary recoils and target fragments in water are evaluated as described in reference 11. The cross sections for protons are also shown for comparison. We note that the most effective energy for neutrons occurs at about 0.45 MeV which corresponds closely to the peak in the low-energy-hydrogen action cross section and is in agreement with the peak neutron effectiveness seen in most experimental studies (ref. 8).

Estimates of Mutation Rates in Space Flight

Establishing the error in estimates of the action cross sections as a function of ion type is difficult because of the protocol used in the experiments as compared with that which occurs in space. The most likely error would occur for the low-LET component in which repair processes show much more vigor in altering experimental results obtained with different protocols such as dose rate or cell-cycle dependence. Goodhead (ref. 16) has discussed the possibility of saturable repair or maximum repair, as in the Michaelis theory (ref. 17), occurring at the dose levels used in ground-based experiments which would lead to overestimation of effects at low dose rates when a linear extrapolation to low doses is used. Also (ref. 2), the possibility of low-dose-rate repair enhancement would correspondingly lead to an underestimation of the low-LET component when a linear extrapolation is used. The track structure model of Katz is based on the premise that the initial slope for low-dose gamma rays is zero, and Katz has recently discussed several experiments that support this premise in reference 18. In the kinetics model of Wilson, Cucinotta, and Shinn (ref. 12), an initial slope arises from misrepair of damage from single photons. The effects of changes in response through the cell cycle must also be considered, as well as the possibility of microgravity altering the cell response.

At low doses where single track effects dominate, we express the mutation rate as a fluence-based risk

coefficient related to the initial slope of the radiation response as

$$M = \sigma_{\text{eff}}\, F(Z, \beta) \tag{4}$$

where F is the particle fluence and σ_{eff} is an effective cross section that includes σ plus a misrepair component. Additivity of radiation effects when assuming a low dose rate would allow us to sum equation (4) over all ion types in the GCR exposure so that

$$M = \sum_j \int dE\ \sigma_{\text{eff}}(Z_j, \beta_j)\, \phi_j(x, E) \tag{5}$$

where ϕ_j is the flux of ions of type j and energy E behind shielding of thickness x. In the kinetics model the effective cross section in equation (4) is separated into two terms; the first term, represented by the Katz model cross section, corresponds to initial damage that is not repairable, and a second term is added to account for misrepair which leads to an initial response for gamma-ray-like radiations such that

$$M = \sigma F + \frac{\alpha_{m1}}{\alpha_1} \sqrt[m]{m!}\, \frac{D_\gamma}{D_0} \tag{6}$$

where D_γ is the gamma-kill dose given by

$$D_\gamma = \left(1 - \frac{\sigma}{\sigma_0}\right) D \tag{7}$$

and α_{m1}/α_1 represents the misrepair rate for single electrons with D denoting the absorbed dose. We note that the coefficient in the second term of equation (6) can be interpreted as the initial slope for gamma rays, where the gamma-ray slope is related to the model parameters by

$$\alpha_\gamma = \frac{\alpha_{m1}}{\alpha_1} \sqrt[m]{m!}\, \frac{1}{D_0} \tag{8}$$

The value of this coefficient can be derived from table 3 and is given as 0.073×10^{-6} cGy^{-1} in comparison with that reported by Tsuboi et al. (refs. 6 and 7) of 0.26×10^{-6} cGy^{-1} and by Cox and Masson (ref. 3) of 0.31×10^{-6} cGy^{-1}. Note that the initial slope estimates for gamma rays are based on experiments above exposures of 1 Gy. In the Katz model this value is, of course, 0. For the present comparison we have also estimated, as described below, the initial slope that would lead to a radiation quality for the HGPRT mutation assay most closely related to the ICRP 60 quality factors (Q) (ref. 19), which is estimated as 0.058×10^{-6} cGy^{-1}. These various estimates of the gamma-ray initial slope for mutation will be utilized in our calculations that follow.

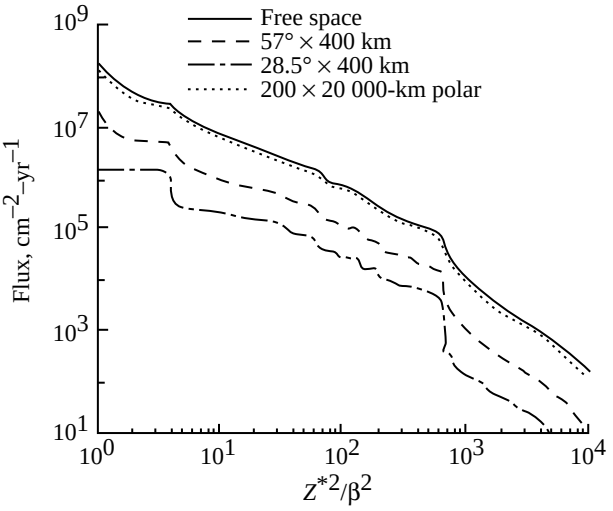


Figure 7. GCR flux spectrum plotted against Z^{*2}/β^2 for free space and several Earth orbits.

The cosmic ray transport code HZETRN (ref. 14) solves the Boltzman equation in the straight-ahead approximation for the energy spectrum of ions as a function of shielding depth in the cosmic ray spectrum up to $Z = 28$ and includes ions produced in fragmentation events from both the projectile and target nuclei. The numerical methods and interaction data base is described in reference 14. For the present calculations, a 1977 solar minimum GCR environment is assumed, as described in reference 20. In figure 7 the integral fluence spectrum is plotted against the track structure parameter Z^{*2}/β^2 (where Z^* is the effective charge number of an ion and β is the velocity) for free space and several trajectories in the Earth's orbit. For reference, an ions minimum value Z^{*2}/β^2 is at Z^2, which allows us to easily find the high-energy peak in the GCR spectrum for various ions.

Values for the absorbed dose and gamma-kill dose behind aluminum and polyethylene shielding are evaluated as described in reference 21 and are given in table 4. Using the modeled cross sections for the mutations in skin fibroblasts, the mutation rates for the GCR exposures are shown in table 5 for different values of the initial slope of gamma-ray-like radiation as described above. The spread in values of the initial gamma-ray slope is seen to represent a change of about a factor of 3 in mutation rates above the estimate using zero initial slope. A breakdown in the individual charge contributions to the total mutation rates using the kinetic model estimates is shown in figures 8 and 9 for aluminum and polyethylene shields, respectively. In table 6 the

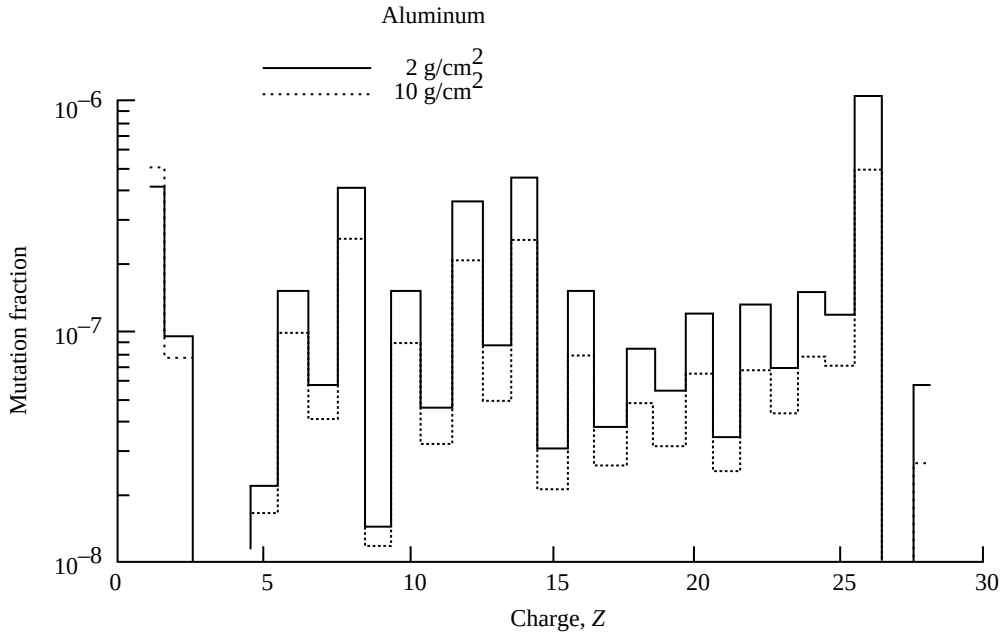


Figure 8. Charge contributions to model GCR HGPRT mutation rates for aluminum shields.

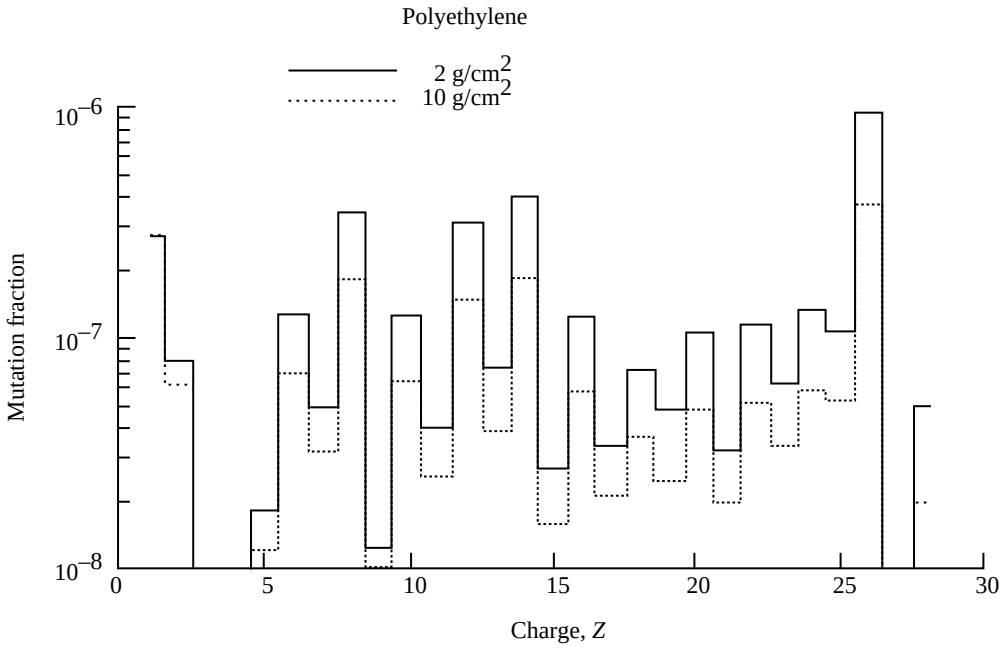


Figure 9. Charge contributions to model GCR HGPRT mutation rates for polyethylene shields.

RBE values are given corresponding to the models in table 5 along with the average value of Q calculated from HZETRN using ICRP 60 (ref. 19).

The initial slope value of 0.058×10^{-6} cGy^{-1} was chosen so that the peak in the RBE maximum curve obtained from equation (5) would most closely correspond to the ICRP 60 quality factor (Q) where experimental determinations are most likely to be made. This is illustrated in figure 10 where Q (or RBE) is plotted against LET along with the predictions of RBE plotted against LET for several ions. For reference, typical values of Q for H, He, Ar, and Fe are highlighted by symbols.

We note that proton experiments are often made in the range from 10 to 30 keV/μm and He experiments are made in the range from 20 to 90 keV/μm,

Table 4. Dose and Gamma-Kill Dose at Solar Minimum

x, g/cm^2	D, cGy	D_γ, cGy
Aluminum shielding		
2	21.5	18.6
5	21.9	19.0
10	22.0	18.8
Polyethylene shielding		
2	18.8	16.4
5	17.4	15.4
10	15.5	13.9

Table 5. Mutation Rates at Solar Minimum

	Mutations $\times 10^{-6}$/yr at an initial slope $\alpha_\gamma \times 10^{-6}$, cGy^{-1}, of—				
x, g/cm^2	0	0.058	0.073	0.26	0.31
Aluminum shielding					
2	4.17	5.25	5.52	9.01	9.94
5	3.46	4.56	4.84	8.40	9.35
10	2.66	3.75	4.03	7.55	8.49
Polyethylene shielding					
2	3.53	4.48	4.73	7.79	8.61
5	2.68	3.57	3.80	6.68	7.45
10	1.85	2.66	2.86	5.46	6.16

Table 6. Comparison of RBE Values for Mutations and Quality Factors

		RBE values at an initial slope $\alpha_\gamma \times 10^{-6}$, cGy^{-1}, of—				
x, g/cm^2	Q	0	0.058	0.073	0.26	0.31
Aluminum shielding						
2	5.4	94	5.0	4.3	2.5	2.3
5	4.2	87	4.3	3.8	2.3	2.2
10	4.0	80	3.7	3.3	2.2	2.1
Polyethylene shielding						
2	5.5	102	4.9	4.2	2.4	2.3
5	4.8	100	4.3	3.8	2.3	2.2
10	4.0	99	3.7	3.3	2.2	2.1

perhaps by using a Van de Graaff generator. Also, high Z measurements with relativistic ions are often made at the Berkeley BEVALAC facility in the range from 100 to 200 keV for Ar and from 180 to 500 keV/μm for Fe. We note that for these types of exposures, the appropriate choice of initial gamma-ray slope leads to a close relationship between Q and the track structure model of RBE. However, large differences will occur in other regions. The most important differences are the reduced effectiveness with increasing charge for a fixed value of LET for relativistic ions and for stopping particles where thin-down occurs, usually above the velocity where the peak in ionization occurs. Also, effectiveness increases for the low-charge ions at energies of a few MeV/amu or less as compared with the quality factor.

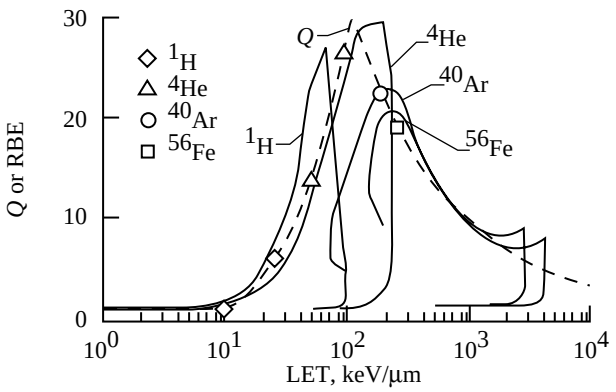


Figure 10. Kinetic track structure model of maximum RBE for several charges versus LET compared with ICRP 60 quality factors (Q).

Concluding Remarks

The mutation rates at the HGPRT locus in human skin and lung fibroblast cell cultures for protons and heavy ions were estimated from experimental data using a kinetics model that utilizes the track structure model of action cross sections of Katz. Parameterizations of the initial slope of the mutation rate were found as a function of ion charge and velocity. We have used these parameterizations and a galactic cosmic ray transport model to estimate the mutation rates to be expected behind typical spacecraft shielding in a free-space exposure. Calculations indicated a mutation rate on the order of 2 to 10 $\times$ 10^{-6} per year for typical spacecraft shielding, with polyethylene shielding being more effective than aluminum by about 20 to 30 percent. Results also indicated that if a linear gamma-ray-like component of an ions action is assumed to be negligible, the mutation rate predicted for the galactic cosmic rays (GCR) would be about one-third that predicted on the basis of a typical finite linear response assumption for the gamma-ray-like component. In contrast to the actual mutation rates predicted, the relative biological effectiveness (RBE) estimate for the GCR would be higher by about a factor of 50 when the gamma-ray-like linear component is assumed to be zero as compared with a typical linear component for gamma rays. These results suggest that the use of a

fluence-based risk system for GCR exposures would result in considerably less uncertainty in model predictions than an RBE approach because of the uncertainty in estimating the gamma-ray initial slope in the experimental biological response.

NASA Langley Research Center
Hampton, VA 23681-0001
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A parametric track structure model is used to estimate the cross section as a function of particle velocity and charge for mutations at the HGPRT locus in human fibroblast cell cultures. Experiments that report the fraction of mutations per surviving cell for human lung and skin fibroblast cells indicate small differences in the mutation cross section for these two cell lines when differences in inactivation rates between these cell lines are considered. Using models of cosmic ray transport, the mutation rate at the HGPRT locus is estimated for cell cultures in space flight and rates of about 2 to 10×10^{-6} per year are found for typical spacecraft shielding. A discussion of how model assumptions may alter the predictions is also presented.

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